IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Cyrus Rustam Kumana and Yok-Lam Kwong

Serial No.: 10/669,869 Art Unit: 1616

Filed: September 23, 2003 Examiner: Frank Choi

For: *Formulation of Oral Compositions Comprising Arsenic Trioxide and Methods of Use Thereof*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. 1.131 AND 1.132

Sir:

We, Cyrus Rustam Kumana and Yok-Lam Kwong, hereby declare that:

1. We are the inventors of the subject matter claimed in the above-identified patent application. We affirm the statements made in our earlier submitted Declarations.

2. We are co-authors of the papers cited by the examiner in the above-identified application mailed March 20, 2008, Kumana CR, Au WY, Lee NS, Kou M, Mak RW, Lam CW, Kwong YL, Eur J Clin Pharmacol. (2002) 58(8):521-6. epub 2002 Oct 11 and Siu CW, Au WY, Yung C, Kumana CR, Lau CP, Kwong YL, Tse HF, Blood (2006) 108(1):103-6. Neither of these are prior art. The other co-authors are not inventors. We alone conceived the idea that it would be advantageous to develop a pure formulation of arsenic-trioxide with known systemic bioavailability, specifically for oral use. We then communicated our ideas to the other co-

authors of the papers. The other co-authors in these papers then assisted only in the reduction to practice of the formulation and treatment, at our direction.

3. Practically all studies of intravenous arsenic trioxide cite a high incidence of QT prolongation (ranging from 40 – 100%) and cardiac arrhythymias.

See, for example, the following publications:

Reference 1

Ohnishi K, Yoshida H, Shigeno K, Nakamura S, Fujisawa S, Naito K, Shinjo K, Fujita Y, Matsui H, Takeshita A, Sugiyama S, Satoh H, Terada H, Ohno R. Prolongation of the QT interval and ventricular tachycardia in patients treated with arsenic trioxide for acute promyelocytic leukemia. Ann Intern Med 2000;133:881-5.

Page 881 clearly states that for five patients given intravenous arsenic trioxide, all developed prolonged QT intervals. Four patients developed ventricular tachycardia and required treatment with anti-arrhythmic agents.

Reference 2

Unnikrishnan D, Dutcher JP, Varshneya N, Lucariello R, Api M, Garl S, Wiernik PH, Chiaramida S. Torsades de pointes in 3 patients with leukemia treated with arsenic trioxide. Blood 2001;97:1514-6.

Page 1514 clearly states that the arsenic trioxide was given as an intravenous infusion Page 1515, table 1, clearly shows that QT prolongation occurred in all three patients given intravenous arsenic trioxide.

Reference 3

Westervelt P, Brown RA, Adkins DR, Khoury H, Curtin P, Hurd D, Luger SM, Ma MK, Ley TJ, DiPersio JF. Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. Blood 2001;98:266-71.

Page 267 clearly states that patients were given a 2-hour intravenous infusion of arsenic trioxide. Page 268 clearly states that QT prolongation was observed and the patient actually died

Reference 4

Soignet SL, Frankel SR, Douer D, Tallman MS, Kantarjian H, Calleja E, Stone RM, Kalaycio M, Scheinberg DA, Steinherz P, Sievers EL, Coutré S, Dahlberg S, Ellison R, Warrell RP Jr. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. J Clin Oncol 2001;19:3852-60.

Page 3852 clearly states that of forty patients given daily intravenous arsenic trioxide infusion, electrocardiographic QT prolongation was common (63%). One patient had an absolute QT interval of > 500 msec and had an asymptomatic 7-beat run of torsades de pointe.

Reference 5

Barbey JT, Pezzullo JC, Soignet SL. Effect of arsenic trioxide on QT interval in patients with advanced malignancies. J Clin Oncol 2003;21:3609-15.

Page 3609 clearly states that prolonged QT intervals developed in 38 patients (26 patients had intervals ≥ 500 milliseconds). Compared with baseline, the heart rate corrected (QTc) interval was prolonged by 30 to 60 milliseconds in 36.6% of treatment courses, and by more than

60 milliseconds in 35.4% of patients. .....This analysis shows that arsenic trioxide can prolong the QTc interval.

Page 3610 then clearly states that patients received daily infusions of arsenic trioxide. Therefore, the results of the paper by Nui et al (mentioned on page 3 of the Office Action) were highly unusual.

4. The studies described in our patent application (see discussion at pages 27-28) demonstrate that orally administered arsenic trioxide avoided the morbidity and mortality linked to QT prolongation and cardiac arrhythmias associated with the use of intravenous arsenic trioxide. We have now gained experience with oral dosing of more than 100 patients, amounting to more than 5000 treatment days without encountering arrhythmia.

5. The peak arsenic levels after the orally administered arsenic trioxide formulation are lower than after IV dosing. This is evident from Figure 2 of our patent application. These figures are also presented and described on page 524 in our paper on the systemic bioavailability of oral arsenic-trioxide (Kumana et al 2000; European Journal of Clinical Pharmacology 58:521-26). The peak levels on day 1 (after 10 mg IV) were substantially higher than the peak levels on day 2 (after the 10 mg oral dose). Sometimes the differences in peak levels after IV and oral dosing were very marked (patients 2 & 8). Moreover, it should be noted that on day 2 the prevailing arsenic levels (including peak levels) were actually the result of the day 2 oral dose + residual arsenic in the blood from IV dosing on day 1. If the oral arsenic had been

administered on day 1, in the absence of antecedent IV dosing, the corresponding post oral dose peak levels would have been even lower.

6. Fowler's solution is not a pure arsenic trioxide solution. Please see the attached references on Fowler's solution: *A Dictionary of Practical Materia Medica* by JH Clarke, and *Drugstore Museum* sponsored by Soderlund Village Drug. Both these sources clearly indicate (see highlighted sections) that Fowler's solution is not entirely pure, and among other substances contains arsenic mainly in the form of potassium arsenite.

7. We declare that all statements made herein of our own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

C R Kumana

CR Kumana Date 13 May 2008

Y L Kwong

YL Kwong Date May 13, 2008.